REMARKS

This preliminary amendment has been submitted to cancel claims 6 and 7. No new matter has been added to this application by way of amendment. As a result of this amendment, claims 1-5 are now pending. It is believed the present application is in condition for allowance, early notification of which is earnestly solicited.

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October 17, 2003

Dated

Respectfully submitted,

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turn below. It will be demonstrated that none of the ISR cited references anticipates or renders obvious the subject matter of the claims of the present application. Each of the cited ISR references are listed in the accompanying Forms 1449A/PTO and 1449B/PTO.

Thibeault *et al.* ("In vitro characterization of a purified NS2/3 protease variant of hepatitis C virus", J. Biol. Chem., vol. 276, no. 49, December 2001, pp. 46678-46684) relates to a purified NS2/3 variant having a minimal catalytic region of 904-1206 retaining auto-cleavage activity. The publication date of December 7, 2001 is later than the priority date of the present application (U.S. provisional application no. 60/256,031; filed December 15, 2000) in which the 904-1206 variant finds literal support for the priority claim. Thus, Thibeault *et al.* does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

Angeletti (International Publication No. WO 01/68818) relates to a NS2/3 polypeptide fragment having an N-terminal boundary between residues 903 and 913 extending to residue 1206 while retaining auto-cleavage activity. This application was published on September 20, 2001 which is after the filing date of the priority application (U.S. provisional application no. 60/256,031; filed December 15, 2000) from which this divisional application claims priority. The present invention is therefore patentable over this reference. Thus, WO 01/68818 does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

Pieroni *et al.* ("In vitro study of the NS2-3 protease of hepatitis C virus", J. Virol., vol. 71, no. 9, September 1997, pp. 6373-6380) describes the production of NS2/NS3 precursor in a latent form in a cell-free translation system and also its reactivation by the addition of detergent. However, the system described does not involve purified enzyme. Thus, Pieroni *et al.* does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

Darke *et al.* ("Inhibition of hepatitis C virus NS2/3 processing by NS4A peptides", J. Biol. Chem., vol. 274, no. 49, December 1999, pp. 34511-34514) reports on processing at the NS2/NS3 junction following expression of the NS2/3 region in a cell-free translation system. However, processing is not reported in an isolated recombinant enzyme as is the case in the

instant invention. Thus, Darke *et al.* does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

Reed *et al.* ("Hepatitis C virus-encoded NS2-3 protease: Cleavage-site mutagenesis and requirements for biomolecular cleavage:, J. Virol. Vol. 69, no. 7, July 1995, pp. 4124-4136) also reports the cleavage activity of NS2/3 protease in transient-expression assays with vaccinia virus T7 hybrid system and not in an isolated / purified enzyme. Thus, Reed *et al.* does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

Santolini *et al.* ("The NS2 protein of hepatitis C virus is a transmembrane polypeptide", J. Virol., vol. 69, no. 12, 1995, pp. 7461-7471) also discloses processing at the NS2/NS3 junction following expression of the NS2/3 region in a cell-free translation system. However, processing is not reported in an isolated recombinant enzyme as is the case in the instant invention. Thus, Santolini *et al.* does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

Chemello *et al.* ("The effect of interferon alfa and ribavirin combination therapy in naive patients with chronic hepatitis C", J. Hepatology, vol. 23, no. Suppl. 3, 1995, pp. 8-12) reports on the effect of interferon alpha and ribavirin combination therapy and does not address the NS2/3 protease activity at all. Thus, Chemello *et al.* does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

Wenzel *et al.* ("Establishment of a cell-based assay for evaluation of compounds against HCV NS2-3 protease activity", Program and Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, vol. 39, 1999, p. 409) discloses a cell-based assay for evaluation of compounds against NS2/3. Once again, the purification and isolation of a catalytically active NS2/3 fragment is not disclosed as is the case in the instant invention. Thus, Wenzel *et al.* does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

Angeletti (International Publication No. WO 97/08304) discloses the expression and isolation of polypeptides with the proteolytic activity of HCV NS3 protease in a pure, catalytically active

form. However, the HCV NS3 protease is a different enzyme than the NS2/3 protease of the instant invention. The NS3 protease is a serine protease that cleaves the downstream junctions of the HCV polyprotein, namely: NS3/NS4A; NS4A/NS4B, NS4B/NS5A and NS5A/NS5B *in trans*. In contrast, the NS2/NS3 protease is a zinc-dependent protease that cleaves the junction between the NS2 protein and the NS3 protein in *cis* (i.e. intramolecularly). The purified catalytically active [904-1206] NS2/3 protease fragment of the instant invention is not disclosed by WO 97/08304. Thus, WO 97/08304 does not anticipate or render obvious, either alone or in combination with the other references, the instant claimed invention.

All of the requirements of 37 C.F.R. § 1.102 and M.P.E.P. § 708.02.VIII having been complied with, applicants respectfully request that this Petition be granted and the instant application be advanced out of turn for accelerated examination according to the provisions of 37 C.F.R. § 1.102 and M.P.E.P. § 708.02.VIII.

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